SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1 NAME OF THE MEDICINAL PRODUCT

REZUROCK 200 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains belumosudil mesilate, equivalent to 200 mg belumosudil.

Excipient(s) with known effect

Sodium less than 1 mmol (23 mg) per dose.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.

Pale yellow, oblong, film-coated tablets debossed with "KDM" on one side and "200" on the other side, with dimensions of 7.40 x 14.77mm.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Rezurock is indicated for the treatment of patients aged 12 years and older with chronic graft-versus-host disease (chronic GVHD) who have received at least two prior lines of systemic therapy.

4.2 Posology and method of administration

Rezurock treatment should be initiated and supervised by physicians experienced in the management of chronic GVHD.

Posology

The recommended dose of Rezurock is 200 mg administered orally once daily at approximately the same time with a meal.

Treatment should continue until disease progression or unacceptable toxicity.

A complete blood cell count and liver function test must be performed before initiating therapy with Rezurock.

Dose modification due to adverse reactions

Perform liver function tests at least monthly throughout treatment (see section 4.4).

The recommended Rezurock dose modifications for hepatotoxicity and other adverse reactions are provided in Table 1.

Table 1: Dose modifications for adverse reactions

Criteria*	**Rezurock Dosage Modifications**
Grade 3 ALT or AST (>5 to 20 × ULN) or Grade 2 bilirubin (>1.5 to 3 × ULN)	Hold Rezurock until recovery to ≤ Grade 1, then resume Rezurock at the recommended dose at physician's discretion.
Grade 4 ALT or AST (>20 × ULN) or Grade ≥3 bilirubin (>3 × ULN)	Permanently discontinue Rezurock.
Other Grade 3 adverse reactions	Hold Rezurock until recovery to ≤ Grade 1, then resume Rezurock at the recommended dose at physician's discretion.
Other Grade 4 adverse reactions	Permanently discontinue Rezurock.

ALT = alanine aminotransferase; AST = aspartate aminotransferase; ULN = upper limit of normal.
*Grade 1 is mild, Grade 2 is moderate, Grade 3 is severe, Grade 4 is life-threatening. Toxicity grades are in accordance with National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.3 (NCI-CTCAE v4.3). See section 4.8.

Dose modification due to drug interactions

Strong CYP3A4 inducers and Proton Pump Inhibitors decrease the exposure of belumosudil (see section 4.5).

Strong CYP3A Inducers

Increase the dosage of Rezurock to 200 mg twice daily when co-administered with strong CYP3A inducers.

Proton Pump Inhibitors

Increase the dosage of Rezurock to 200 mg twice daily when co-administered with proton pump inhibitors.

Delayed or missed dose

If a dose is missed or delayed for less than 12 hours after the scheduled dose, the dose should be taken as soon as possible on the same day with a return to the normal schedule the following day.

If a dose is missed or delayed for more than 12 hours after the scheduled dose, the dose should be taken at the usual time the following day.

If a patient vomits following the intake of a dose, the next dose should be taken at the usual time the following day.

Patients should not take extra doses to make up the missed dose.

Special populations

Hepatic impairment

Use in patients with moderate hepatic impairment (Child-Pugh B) or severe hepatic impairment
(Child-Pugh C) without liver GVHD is not recommended (see section 5.2).
Dose modification is not recommended when administering belumosudil to patients with mild hepatic impairment (Child-Pugh A).

Monitor patients frequently for adverse reactions.

Renal impairment

No dose modification of Rezurock is required in patients with mild or moderate renal impairment (creatinine clearance $\geq$ 30 mL/min).

No data are available for patients with severe renal impairment (creatinine clearance < 30 mL/min) or for patients with end-stage renal disease on dialysis (see sections 5.1 and 5.2). Use with caution.

Elderly patients (≥65 years)

No additional dose adjustments are recommended for elderly patients (see sections 5.1 and 5.2).

Paediatric population

The posology is the same in adults and adolescents aged 12 to 18 years.

The safety and efficacy of Rezurock in children and adolescents aged below 12 years of age have not been established. No data are available (see section 5.1).

Method of administration

For oral use.

Rezurock should be taken at approximately the same time each day with a meal (see section 5.2).

The film-coated tablet should not be broken, crushed or chewed.

4.3 Contraindications

Pregnancy.

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Women of childbearing potential

Women of childbearing potential should be advised to avoid becoming pregnant while taking belumosudil and of the potential risk to a foetus, and to have a pregnancy test prior to starting treatment with belumosudil.

Women of childbearing potential must use a highly effective method of contraception during treatment with belumosudil and for at least one week after the last dose of belumosudil (see sections 4.6 and 5.3).

Male patients

Male patients with female partners of childbearing potential should be advised that their female partners should avoid becoming pregnant while taking belumosudil and of the potential risk to a foetus.

Males with female partners of childbearing potential must use a highly effective method of contraception during treatment with belumosudil and for at least a week after the last dose of belumosudil (see sections 4.6 and 5.3).

Breast-feeding

Breast-feeding is not recommended during treatment with belumosudil and for at least one week after the last dose (see section 4.6).

Hepatotoxicity

Increases in liver function tests were observed in clinical studies with belumosudil and generally occurred early during treatment with the incidence decreasing thereafter (see section 4.8). Liver function tests should be performed prior to the initiation of treatment with belumosudil and monitored at least monthly during treatment with belumosudil and the dose should be adjusted for ≥ Grade 2 toxicities (see section 4.2)

4.5 Interaction with other medicinal products and other forms of interaction

Effect of CYP3A inhibitors on belumosudil

The co-administration of multiple doses of itraconazole (a strong CYP3A inhibitor) did not alter exposure to belumosudil to any clinically relevant extent.

Effect of CYP3A inducers on belumosudil

The co-administration of multiple doses of rifampin (a strong CYP3A4 inducer) decreased belumosudil C_{max} by 59% and AUC by 72%. The co-administration of strong CYP3A4 inducers with belumosudil may decrease belumosudil exposure. Increase the dose of belumosudil to 200 mg twice daily (see section 4.2).

The co-administration of moderate CYP3A4 inducers e.g., efavirenz is predicted to have a reduced effect on belumosudil as compared to strong CYP3A4 inducers. The co-administration of moderate CYP3A4 inducers with belumosudil may decrease belumosudil exposure. No dose adjustment is recommended.

Effect of proton pump inhibitors on belumosudil

The co-administration of multiple doses of rabeprazole decreased belumosudil C_{max} by 87% and AUC by 80%. The co-administration of multiple doses of omeprazole decreased belumosudil C_{max} by 68% and AUC by 47%. The co-administration of proton pump inhibitors with belumosudil may decrease belumosudil exposure. Increase the dose of belumosudil to 200 mg twice daily (see section 4.2).

Effect of other gastric acid reducing agents on belumosudil

The co-administration of belumosudil with gastric acid reducing agents other than proton pump inhibitors may decrease belumosudil exposure. No dose adjustment is recommended, however belumosudil and the gastric acid reducing agent should be taken 12 hours apart.

In vitro studies
Effect of belumosudil on CYP3A substrates

The co-administration of belumosudil is predicted to increase midazolam (a sensitive CYP3A substrate) C_{max} and AUC approximately 1.30- and 1.65-fold, respectively. No dose adjustment is recommended.

The co-administration of belumosudil may increase exposure of sensitive CYP3A4 substrates with a narrow therapeutic index such as ciclosporin and tacrolimus. No dose adjustment is recommended.

Effect of belumosudil on CYP2C9 substrates

The co-administration of belumosudil is not expected to have clinically meaningful effect on the exposure of CYP2C9 substrates (such as warfarin).

Effect of belumosudil on CYP2C8 substrates

The co-administration of belumosudil is not expected to have clinically meaningful effect on the exposure of CYP2C8 substrates that are not an OATP1B1 substrate.

Effect of belumosudil on UGT1A1 substrates

Belumosudil is a weak inhibitor of UGT1A1, the clinical consequences are not known.

Transporters

Avoid coadministration of belumosudil with P-gp (e.g. dabigatran), OATP1B1, and BCRP substrates (e.g. rosuvastatin), for which minimal concentration changes may lead to serious toxicities. If coadministration cannot be avoided, decrease the P-gp, OATP1B1, and BCRP substrates dosage(s) in accordance with the respective Prescribing Information.

Belumosudil is an inhibitor of P-gp, OATP1B1, and BCRP. Coadministration of belumosudil with P- gp, OATP1B1, and BCRP substrates increased their plasma concentrations (see section 5.2), which may increase the risk of adverse reactions related to these substrates.

Certain CYP1A2 substrates

Caution should be advised when co-administering belumosudil with sensitive CYP1A2 substrates, for which minimal concentration changes may lead to serious toxicities (for examples of sensitive CYP1A2 substrates see Section 5.2 Pharmacokinetic properties).

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no data on the use of belumosudil in pregnant women.

Belumosudil can cause foetal harm based on findings from animal studies (see section 5.3) and its mechanism of action. In pregnant rats and rabbits, oral administration of belumosudil resulted in maternal and/or foetal toxicity at doses below the recommended human dose. As a precautionary measure, belumosudil is contraindicated in pregnancy (see section 4.3).

Women of childbearing potential/Contraception in males and females

Women of childbearing potential should be informed that animal studies show belumosudil to be harmful to the developing foetus. Women of childbearing potential must have their pregnancy status verified prior to initiating treatment with belumosudil, and must use a reliable and highly effective method of contraception during treatment with belumosudil and for at least one week after the last dose of belumosudil. In case pregnancy should occur during treatment with belumosudil, a risk/benefit evaluation must be carried out on an individual basis with careful counselling regarding potential risks to the foetus (see sections 4.4 and 5.3).

Male patients with female partners of childbearing potential should be advised that their female partners should avoid becoming pregnant while taking belumosudil and of the potential risks to a foetus.

Male patients with female partners of childbearing potential must use a highly effective method of contraception during treatment and for at least one week after the last dose of belumosudil (see section 4.4).

Breast-feeding

It is unknown whether belumosudil or its metabolites are excreted in human milk. No data are available regarding the presence of belumosudil or its metabolites in animal or human milk or its effects on the breast-fed child, or on

milk production. A risk to the infant cannot be excluded. Because of the potential for serious adverse reactions in a breast-fed child, breast-feeding should be discontinued during treatment with belumosudil and for at least one week after the last dose (see section 4.4).

Fertility

There are no human data on the effect of belumosudil on fertility.

Belumosudil repeat dose toxicity studies in rats demonstrated effects of general toxicity manifesting low body weight that may lead to impairment of female fertility (see section 5.3).

Based on testicular findings from rats and dogs, belumosudil may impair male fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

Belumosudil may cause fatigue and dizziness (see section 4.8). Patients should be advised not to drive or operate machines if they experience these symptoms.

4.8 Undesirable effects

Summary of safety profile

The overall safety profile of belumosudil in chronic graft-versus-host-disease is based on data from 186 patients from two clinical trials, KD025-208 and KD025-213.

The most common adverse reactions (≥5%) were asthenia (21.0%), nausea (12.4%), liver function test abnormalities of elevation of AST (7.5%), elevation of ALT (7.0%) and elevation of GGT (4.8%), headache (8.6%), diarrhoea (7.0%) and musculoskeletal pain (5.9%). The most common Grade 3 or 4 adverse reaction (≥ 2%) was asthenia (2.7%). Serious adverse reactions were pneumonia (1.1%), cellulitis, infectious colitis, staphylococcal bacteraemia, diarrhoea, nausea, vomiting, microangiopathic haemolytic anaemia, multiple organ dysfunction syndrome and cGVHD (0.5% each).

The most common adverse reactions leading to discontinuation were nausea (2.4%) and headache (2.4%). Adverse reactions leading to dose interruption occurred in 9.6% of patients and were mainly investigations (3.6%), including ALT increased, GGT increased and blood creatine phosphokinase increased (1.2% each), and infections (2.4%).

Tabulated list of adverse reactions

Table 2 presents the frequency category for adverse reactions reported in the open-label clinical trials (studies KD025-208 and KD025-213) with belumosudil. A total of 186 adult patients with chronic GVHD were treated with belumosudil 200 mg once daily (N=83), 200 mg twice daily (N=82), or 400 mg once daily (N=21) (see section 5.1). The median duration of treatment of the 83 patients with 200 mg once daily belumosudil was 9.2 months (range 0.5 to 44.7 months) and in the 186 patients across the three dosing cohorts was 9.89 months (range 0.39 to 44.71 months).

The frequency of adverse reactions are defined as follows:

Very common: (≥1/10)
Common: (≥1/100 to <1/10)
Uncommon: (≥1/1000 to <1/100)
Rare: (≥1/10,000 to <1/1000)
Very rare: (<1/10,000)
Not known: (cannot be estimated from the available data)

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 2: Adverse reactions (≥2%) in patients with chronic GVHD who received belumosudil

Adverse Reaction	**Rezurock Pooled chronic GVHD (N=186)**		
	All severity grades Frequency category	**All grades[a] (%)**	**Grade 3-4[a] (%)**
Infections and infestations			
Upper respiratory tract infections[b]	Common	7 (3.8%)	0
Lower respiratory tract infections[c]	Common	5 (2.7%)	2 (1.1%)
Blood and lymphatic system disorders			
Anaemia*	Common	6 (3.2%)	1 (0.5%)
Leukopenia[d]*	Common	9 (4.8%)	3 (1.6%)
Platelet count decreased	Common	5 (2.7%)	0
Metabolism and nutrition disorders			
Decreased appetite	Common	7 (3.8%)	1 (0.5%)
Hyperglycaemia	Common	7 (3.8%)	0
Nervous system disorders			

	Rezurock Pooled chronic GVHD (N=186)		
Headache	Common	16 (8.6%)	1 (0.5%)
Neuropathy peripheral	Common	6 (3.2%)	0
Dizziness	Common	4 (2.2%)	0
Vascular disorders			
Hypertension	Common	6 (3.2%)	3 (1.6%)
Respiratory, thoracic and mediastinal disorders			
Dyspnea[e]	Common	7 (3.8%)	0
Cough[f]	Common	7 (3.8%)	0
Gastrointestinal disorders			
Nausea	Very common	23 (12.4%)	2 (1.1%)
Diarrhoea	Common	13 (7.0%)	2 (1.1%)
Vomiting	Common	9 (4.8%)	1 (0.5%)
Abdominal pain[g]	Common	5 (2.7%)	0
Constipation	Common	5 (2.7%)	1 (0.5%)
Hepatobiliary disorders			
Aspartate aminotransferase increased	Common	14 (7.5%)	3 (1.6%)
Alanine aminotransferase increased	Common	13 (7.0%)	2 (1.1%)
Gamma-glutamyltransferase increased	Common	9 (4.8%)	2 (1.1%)
Skin and subcutaneous tissue disorders			
Pruritus	Common	5 (2.7%)	0
Musculoskeletal and connective tissue disorders			
Musculoskeletal pain[h]	Common	11 (5.9%)	0
Muscle spasms	Common	8 (4.3%)	0
Blood alkaline phosphatase increased	Common	7 (3.8%)	0
Blood creatine phosphokinase increased	Common	4 (2.2%)	1 (0.5%)
Renal and urinary disorders			
Blood creatinine increased	Common	4 (2.2%)	0

	Rezurock Pooled chronic GVHD (N=186)		
General disorders and administration site conditions			
Asthenia[i]	Very common	39 (21.0%)	5 (2.7%)
Oedema[j]	Common	9 (4.8%)	0
Pyrexia	Common	3 (1.6%)	0
Investigations			
Weight decreased	Common	6 (3.2%)	0

[a] *National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 5.0 and version 4.03 for studies KD025-208 and KD025-213, respectively*
[b] includes upper respiratory tract infection, sinusitis.
[c] includes pneumonia, bronchitis, bronchitis viral.
[d] includes leukopenia, neutropenia, neutrophil count decreased, white blood cell count decreased, lymphocyte count decreased.
[e] includes dyspnea, dyspnea exertional.
[f] includes cough, productive cough.
[g] includes abdominal pain, abdominal pain upper.
[h] includes arthralgia, pain in extremity, back pain, neck pain.
[i] includes fatigue, asthenia, malaise.
[j] includes oedema peripheral, face oedema, localized oedema, swelling.
* See description of selected adverse reactions.

Description of selected adverse reactions

Hepatobiliary disorders

Elevations of liver enzymes were reported in patients treated with belumosudil in clinical trials. In two randomised, open label, multi-centre clinical trials in patients with cGVHD (studies KD025-208 and KD025-213), any grade laboratory abnormalities of increased AST, increased ALT and increased GGT occurred in 7.5%, 7.0% and 4.8%, respectively, of patients receiving belumosudil. Grade ≥ 3 laboratory abnormalities of increased AST, increased ALT and increased GGT occurred in 1.6%, 1.1% and 1.1%, respectively, of patients receiving belumosudil. Events resolved with few drug discontinuations, drug interruptions or dose reductions. The events generally occurred early during belumosudil treatment with the incidence decreasing thereafter. For recommended dosage modifications following elevations of liver enzymes see section 4.2. For recommended monitoring of liver enzymes see section 4.4.

Blood and lymphatic disorders

In the randomised, open label, multi-centre clinical trials in patients with cGVHD (studies KD025-208 and KD025-213), any grade anaemia and leukopenia occurred in 3.2% and 4.8%, respectively, of patients receiving belumosudil. Grade ≥ 3 events of anaemia and leukopenia occurred in 0.5% and 1.6%, respectively, of patients receiving belumosudil. Grade 3 cytopenias were often associated with relapse of the underlying malignancy.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected new or serious adverse reactions via the Yellow Card Scheme. You can find information on this at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

No cases of overdose have been reported.

There is no specific experience in the management of belumosudil overdose in patients. There is no known antidote for overdoses with belumosudil. Single doses up to 1000 mg have been given with acceptable tolerability in healthy volunteers. Appropriate supportive treatment should be given.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunosuppressants, selective immunosuppressants, ATC code: L04AA48.

Mechanism of action

Belumosudil is a potent and selective Rho-associated, coiled-coil containing protein kinase-2 (ROCK2) inhibitor that mediates signalling in immune cellular function and fibrotic pathways. In vivo, belumosudil has demonstrated activity in a variety of clinically relevant animal models of disease including chronic GVHD.

Pharmacodynamic effects

Cardiac Electrophysiology

At a dose of 5 times the recommended dose, belumosudil does not prolong the QT interval to any clinically relevant extent.

Clinical efficacy and safety

Two open-label Phase 2 studies (studies KD025-208 and KD025-213) were conducted in patients with chronic GVHD.

Study KD025-213

Study KD025-213 (N=131) was a randomized, open-label, multicentre study of belumosudil for treatment of patients with chronic GVHD. Patients were eligible for the study if they had received 2 to 5 prior lines of systemic therapy and required additional therapy. Patients received a stable dose of corticosteroids for two weeks prior to entry to the study. Patients were randomised 1:1 to receive belumosudil dosed orally at 200 mg once daily or 200 mg twice daily. Randomization was stratified according to prior cGVHD treatment with ibrutinib (yes/no) and severe cGVHD (yes/no).

Where patients were on a stable dose/schedule of standard of care therapies for chronic GVHD, concomitant use of these was permitted, including local and topical treatments and ECP. Transient increases in corticosteroid dosing (that did not exceed 1 mg/kg/day prednisone equivalent) were permitted for the treatment of cGVHD flare, but the dose must have been reduced back to the pre-randomization dose within 6 weeks. If the dose remained elevated for more than 6 weeks, this was considered a belumosudil treatment failure. More than 2 episodes of cGVHD flare that required increased corticosteroid therapy in the first 6 months of belumosudil treatment was also considered a belumosudil treatment failure. Initiation of one or more new systemic therapies for chronic GVHD indicated a new line of therapy and was classified as a treatment failure.

Of patients enrolled in the study, the median age was 55 years (range 21 to 77 years), 57% of patients were male and 85% were white. The majority (67%) of patients had severe cGVHD disease and 73% of patients were refractory to their last systemic therapy prior to enrolling in the study. The most common underlying malignancies leading to transplantation were acute myeloid leukaemia, acute lymphocytic leukaemia and myelodysplastic syndromes. The organs involved at baseline were skin (83%), joints/fascia (76%), eyes (74%), lung (36%), mouth (54%), oesophagus (24%), upper GI (17%), lower GI (10%) and liver (10%), and 51% of patients had 4 or more organs involved. The most common prior systemic therapy was corticosteroids (98%), followed by calcineurin inhibitors (tacrolimus 62% and sirolimus 47%), ECP (48%), ibrutinib (34%) and ruxolitinib (29%). The median prior lines of therapy was 3 (range 2-6).

The primary efficacy endpoint was the overall response rate (ORR), defined as the proportion of subjects who achieved a complete response or a partial response according to the 2014 NIH Consensus Development Project on Criteria for Clinical Trials in chronic GVHD. Responses were assessed by investigators. Secondary endpoints included duration of response, changes in symptom burden/bother using the Lee Symptom Scale Score (LSS) and time to next treatment.

Study KD025-213 met its primary objective. For the 200 mg once daily dose, the ORR (data cut-off: 19-Aug-2020) was 74% (62-84%); 6% of patients achieved a CR and 68% of patients achieved a PR. Responses, including complete responses, were achieved across all organs involved (skin, eyes, joints/fascia, mouth, lung, oesophagus, upper GI, lower GI and liver). Duration of response (defined as the time from first ORR response to progression of disease in any organ measured in comparison to nadir, new systemic therapy, or death whichever comes first) was 8 weeks (95% CI 4-64 weeks).

Results for Study KD025-213 at the 200 mg once daily belumosudil dose are presented in Table 3.

Table 3: Best overall response rate and other efficacy results in Study KD025-213

	Rezurock (N=131)
	200 mg once daily (N=65)
Overall response rate (%)	73.8
95% CI (%)	(61.5, 84.0)
Complete response (%)	6.2
Partial response (%)	67.7
K-M duration of response, median, weeks (95% CI)	8.1 (3.7, 64.3)
Time to response, median, weeks (range)	4.4 (3.7, 40.6)
K-M time to next treatment, median, months (95% CI)	NA (13.73, NA)
≥7 Point decrease in Lee Symptom Scale Score on consecutive assessments, n (%)	28 (43)
Discontinued corticosteroid during Belumosudil treatment, n (%)	12 (19)

CI = Confidence interval; K-M = Kaplan Meier; NR = Not reached.

For the 200 mg twice daily dose, the ORR was 77.3% (95% CI 65.3%, 86.7%) and the DOR (defined as the time from first ORR response to progression of disease in any organ measured in comparison to nadir, new systemic therapy, or death whichever comes first) was 8 weeks (95% CI 2-81 weeks).

Study KD025-208

Study KD025-208 (N=54) was a dose-escalation, open-label, multicentre study of belumosudil for treatment of patients with chronic GVHD who had received 1 to 3 prior lines of systemic therapy and required additional therapy. Belumosudil was administered orally at 200 mg once daily (N=17), 200 mg twice daily (N=16), or 400 mg once daily (N=21).

Where patients were on a stable dose/schedule of standard of care therapies for chronic GVHD, concomitant use of these was permitted, including corticosteroids and calcineurin inhibitors. Initiation of one or more new systemic therapies for chronic GVHD indicated a new line of therapy and was classified as a treatment failure.

Of patients enrolled in the study, the median age was 52 years (range 20 to 75 years), 63% of patients were male and 87% were white. The majority (78%) of patients had severe cGVHD disease and 73% of patients were refractory to their last systemic therapy prior to enrolling in the study. The most common underlying malignancies leading to transplantation were acute myeloid leukaemia, acute lymphocytic leukaemia and myelodysplastic syndromes. The organs involved at baseline were eyes (78%), skin (74%), mouth (65%), joints/fascia (63%), lung (32%), upper GI (15%), oesophagus (11%), lower GI (7%), and liver (4%), and 50% of patients had 4 or more organs involved. The most common prior systemic therapy was corticosteroids (100%), followed by calcineurin inhibitors (tacrolimus 48% and sirolimus 44%), rituximab (30%), and ECP (28%). The median number of prior lines of therapy was 2.5 (range 1-4).

The primary efficacy endpoint was the overall response rate (ORR), defined as the proportion of subjects who achieved a complete response or a partial response according to the 2014 NIH Consensus Development Project on Criteria for Clinical Trials in chronic GVHD. Responses were assessed by investigators. Secondary endpoints included duration of response, failure free survival and time to next treatment.

Study KD025-208 met its primary objective. For the 200 mg once daily dose, the ORR was 64.7% (95% CI 38.3%, 85.8%). Responses (partial response) were achieved across all organs involved, there were no complete responses reported. Duration of response (defined as the time from first ORR response to progression of disease in any organ measured in comparison to nadir, new systemic therapy, or death whichever comes first) was 19 weeks (95% CI 7-128 weeks).

Safety and efficacy in older patients

Of the 186 patients with chronic GVHD in clinical studies of belumosudil, 25.8% were 65 years and older. No overall differences in safety or effectiveness of belumosudil were observed between these patients and younger patients.

Paediatric population

The Medicines and Healthcare Products Regulatory Agency has deferred the obligation to submit the results of studies with Rezurock.

5.2 Pharmacokinetic properties

Absorption

Median T_{max} of belumosudil across studies was approximately 3 hours. Following a single oral dose of belumosudil 200 mg, mean absorption (% coefficient of variation) was 64% (17%).

Effect of Food

In healthy subjects, the administration of a single 200 mg dose of belumosudil with a high-fat and high-calorie meal (800 to 1,000 calories with approximately 50% of total caloric content of the meal from fat) increased belumosudil C_{max} to 2.2 times that following fasted administration and AUC to 2 times that following fasted administration. Median T_{max} was delayed 0.5 hours.

The mean steady-state AUC (% coefficient of variation) observed in patients with chronic GVHD receiving 200 mg once daily administered with food was 22700 (48%) h•ng/mL; mean steady-state C_{max} was 2390 (44%) ng/mL. With once daily administration, steady-state concentrations of belumosudil were achieved with an accumulation ratio of 1.4.

Distribution

Pharmacokinetics were described by a two compartmental model with a distribution half-life of 1.8 h. Belumosudil volume of distribution of the central compartment (% coefficient of variation, CV) was 29.7 L (143%). In in vitro preparations, binding to human serum albumin was 99.9% and binding to human α1-acid glycoprotein was 98.6%.

Biotransformation

Based on in vitro assessment, CYP3A4 was the predominant CYP isoform responsible for the metabolism of belumosudil, although CYP2C8, CYP2D6 and UGT1A9 contributed to a lesser extent.

Elimination

Population PK modelling results in chronic GVHD patients showed that belumosudil elimination half-life (% coefficient of variation, CV) was 19.0 h (39%). Belumosudil clearance (% coefficient of variation, CV) was 9.83 L/h (46%).

The Human Mass Balance study results indicated that faecal excretion is the major route of excretion (85% of the dose). Of the dose recovered in faeces, 30% was parent belumosudil. Less than 5% of the dose was recovered in urine.

Linearity/non-linearity of dose

Exposure to belumosudil (C_{max} and AUC) appears to be slightly greater than dose proportional over the 20 to 500 mg once daily dose range, but less than dose-proportional for doses above 500 mg in healthy subjects. In chronic

GVHD subjects, the exposure increase between 200 and 400 mg is approximately proportional.

Special populations

No clinically relevant differences in belumosudil pharmacokinetics were observed with regard to age, race, sex, weight or renal impairment (mild or moderate; severe renal impairment has not been studied).

Hepatic impairment

Following a single 200 mg dose of belumosudil, changes in belumosudil exposure in subjects with varying degrees of hepatic impairment based on Child-Pugh score without liver GVHD relative to subjects with normal hepatic function is shown in Table 4

Table 4: Effect of Varying Degrees of Hepatic Impairment on Belumosudil Exposure

Hepatic Impairment Category	**Changes in Belumosudil Exposure in Subjects with Hepatic Impairment Compared to Subjects with Normal Hepatic Function**			
	Total (Free + Bound) Concentrations		**Unbound Concentrations**	
	C_{max}	**AUC**	**C_{max}**	**AUC**
Mild (Child-Pugh A)	1.2-fold increase	1.4-fold increase	0.9-fold decrease	0.8-fold decrease
Moderate (Child-Pugh B)	0.9-fold decrease	1.5-fold increase	0.9-fold decrease	1.4-fold decrease
Severe (Child-Pugh C)	1.3-fold increase	4.2-fold increase	5.4-fold increase	16.3-fold increase

Drug Interaction Studies

Effects of Other Drugs on Belumosudil

Strong Cytochrome P450 (CYP) 3A Inhibitors: There was no clinically meaningful effect on
belumosudil exposure when co-administered with itraconazole in healthy subjects.

Strong CYP3A4 Inducers: Coadministration of rifampin decreased belumosudil C_{max} by 59% and AUC by 72% in healthy subjects.

Moderate CYP3A Inducers: Coadministration of efavirenz is predicted to decrease belumosudil C_{max} by 19% and AUC by 35% in healthy subjects.

Proton Pump Inhibitors: Coadministration of rabeprazole decreased belumosudil C_{max} by 87% and AUC by 80%, and coadministration of omeprazole decreased belumosudil C_{max} by 68% and AUC by 47% in healthy subjects.

Effects of Belumosudil on Other Drugs

Enzyme Systems
CYP3A Substrates: Coadministration of belumosudil is predicted to increase midazolam (a sensitive CYP3A substrate) C_{max} and AUC approximately 1.30- and 1.65-fold, respectively.

CYP2C9 Substrates: Coadministration of belumosudil is not expected to have clinically meaningful effect on the exposure of CYP2C9 substrates (such as warfarin).

CYP2C8 Substrates: Coadministration of belumosudil is not expected to have clinically meaningful effect on the exposure of CYP2C8 substrates that are not an OATP1B1 substrate.

CYP1A2 Substrates with a Narrow Therapeutic Index: Belumosudil is predicted to increase theophylline AUC by 40%. Caution should be advised when co-administering belumosudil with CYP1A2 substrates with a narrow therapeutic index (e.g., theophylline, warfarin, tizanidine or pomalidomide).

Transporter systems
OATP1B1/BCRP substrates: Coadministration of belumosudil increases rosuvastatin C_{max} and AUC by 3.6 and 4.6-fold, respectively (see section 4.5).

P-glycoprotein (P-gp) substrates: Coadministration of belumosudil increased the exposure of
dabigatran by 2-fold.

In Vitro Studies
Enzymes Systems: Belumosudil is an inhibitor of CYP1A2, CYP2C19, CYP2D6, UGT1A1, CYP3A4 and UGT1A9.

Transporter Systems: Belumosudil is a substrate of P-glycoprotein (P-gp). Belumosudil inhibits
BCRP, P-gp, and OATP1B1 at clinically relevant concentrations.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, genotoxicity, carcinogenic potential.

Belumosudil did not result in any carcinogenic effect in a 6-month CByB6F1-Tg (HRAS)2Jic
hemizygous mouse study.

Belumosudil was not mutagenic in an in vitro bacterial mutagenicity (Ames) assay. Belumosudil was not clastogenic in either an in vitro chromosome

aberration assay in mammalian (CHO) cells or an in vivo mouse bone marrow micronucleus assay.

Belumosudil repeat dose toxicity studies in rats demonstrated effects of general toxicity manifesting low body weight that may lead to impairment of female fertility. Based on testicular findings from rats and dogs, belumosudil may impair male fertility.

Repeated oral dose studies with belumosudil of up to 6-months in rats and 3-months in the dog were conducted. The No-Observed-Adverse-Effect-Level (NOAEL) in the 6-month rat study with 4-weeks recovery was < 50 mg/kg/day [male] /125 mg/kg/day [female] (<1.1- to 7.4-fold the AUC at the human recommended dose). In a 3-month dog study, belumosudil was administered at 35, 70, and 125 mg/kg/day with 4 weeks of recovery, the NOAEL was <35 mg/kg/day [male] and 35 mg/kg/day[female] (~1-fold human AUC).

Following administration of belumosudil to rats and/or dogs, the adverse effects observed in one or both species included toxicities in the gastrointestinal (GI) tract (emesis, loose stools, and/or abnormal black contents, increase in salivation), liver (elevated liver enzymes, hypertrophy/increased organ weight, and cholestasis/inflammation), kidney (increased blood urea nitrogen [BUN], tubular changes, pigmentation, intracellular protein droplets in the epithelium), hemolymphoid system (regenerative anemia), and reproductive system.

Adverse changes in male and female reproductive organs also occurred in general 3-month and 6- month toxicology studies. In males, findings included spermatozoa degeneration at a belumosudil dose of ≥50 mg/kg/day in rats and ≥35 mg/kg/day in dogs. The exposure (AUC) at the doses of 50 mg/kg/day in male rats and 35 mg/kg/day in male dogs is 1.1-fold the clinical exposure at the recommended human dose of 200 mg/day. Changes were reversible in dogs but not fully reversible in rats. In female rats, changes included lower uterine weights that correlated with uterine/cervical hypoplasia and decreased follicular development in ovaries related to adverse body weight reduction due to lower food consumption at 275 mg/kg/day in rats. Changes were fully reversed during the 4- week recovery period.

In a female rat fertility and early emrbyonic development study, belumosudil was administered to female rats 14 days prior to mating and up to gestation day 7. Belumosudil had no effect on fertility or reproductive function of female rats at doses of 50, 150 or 275 mg/kg/day. However, in female rats at a dose of 275 mg/kg/day resulted in maternal toxicity and increased post-implantation loss/resorptions and decrease in the number of viable foetuses. The exposure (AUC) at the dose of 275 mg/kg/day is approximately 9.4 times the clinical exposure (AUC) at the maximum recommended dose of 200 mg daily.

In a male rat fertility and early embryonic development study, belumosudil was administered to male rats 70 days prior to and throughout mating to non-treated female rats. Belumosudil had no effects on fertility or reproductive function in male rats at doses of 50 and 150 mg/kg/day. However, a dose of 275 mg/kg/day resulted in generalized toxicity, reduced male fertility, abnormal sperm findings

(reduced motility, reduced concentration and increased percentage of abnormal sperm), and testes/epididymis organ changes. The exposure (AUC) at the dose of 275 mg/kg/day is approximately 8.6 times the clinical exposure at the maximum recommended dose of 200 mg daily.

Embryo-foetal development studies were conducted in rats with administration of belumosudil to pregnant animals during the period of organogenesis at oral doses of 25, 50, 150, and 300 mg/kg/day in an exploratory pilot study and doses of 15, 50, and 150 mg/kg/day in a pivotal study. In the exploratory study, maternal toxicity and embryo-foetal developmental effects were observed. Maternal toxicity (reduced body weight gain) occurred at 150 and 300 mg/kg/day doses. Increased post- implantation loss occurred at 50 and 300 mg/kg/day. Foetal external malformations were observed at ≥50 mg/kg/day and included absence of anus and tail, omphalocele, and dome shaped head. The exposure (AUC) at 50 mg/kg/day in rats is approximately 1.4-fold the human exposure at the recommended dose of 200 mg daily.

In pregnant rabbits, oral administration of belumosudil during the period of organogenesis resulted in maternal toxicity (body weight loss, reduced body weight gain, low food consumption and mortality) at doses ≥ 125 mg/kg/day. Foetal effects included abortions, increased post-implantation loss, decreased percentage of live foetuses, decreased foetal body weight, and skeletal/external malformations in foetuses at doses ≥ 50 mg/kg/day (approximately 0.08-fold the human exposure at the recommended dose based on AUC).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Microcrystalline cellulose

Hypromellose

Croscarmellose sodium

Colloidal silicon dioxide

Magnesium stearate

Tablet coating

Polyvinyl alcohol (E1203)

Polyethylene glycol (E1521)

Talc (E553b)

Titanium dioxide (E171)

Yellow iron oxide (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not store above 25°C.

Dispense to patient in original packaging only.

Store in the original package in order to protect from moisture.

Replace cap securely each time after opening. Do not discard desiccant.

6.5 Nature and contents of container

High-density polyethylene bottle with a child-resistant closure and a silica gel desiccant in a pack size of 30 film-coated tablets.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Aventis Pharma Limited,
410 Thames Valley Park Drive,
Reading,

Berkshire, RG6 1PT,
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

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